Balancing a biologics pipeline portfolio

Why biosuperiors represent a solid counterbalance to an innovative research and development programme

Research into groundbreaking biologic therapies has significantly shifted the diagnosis and treatment paradigms for many disease categories, particularly in oncology, autoimmune, inflammation and neurology. Discovering and developing an innovative, first-in-class biologic has the potential to offer patients significant benefits as well as add substantially to a developer's bottom-line as these medicines often become the new standard of care. But reaching this goal requires a difficult and seemingly insurmountable journey through the laboratory and the varying phases of clinical research.

By Dr Herren Wu

Drug discovery and development is a highly complex and risky business. For every 5,000 pharmaceutical and biologic discoveries in pre-clinical testing, an estimated one to five products are ultimately approved for human use. Biologics currently represent a smaller portion of this pool of approved products. In spite of the risks involved, R&D programmes continue focusing on creating first-in-class therapies because of the potential gains, for the developers and the physician and patients they serve.

The high chance of failure associated with the biologic research and development process is making it necessary for many companies to diversify their resources in order to create a more balanced pipeline portfolio. The development of 'biosimilars' and 'biosuperiors' offers the potential to counterbalance the high risk nature of drug discovery and development. With the introduction of these types of biologics, some drug developers may now be wondering what is the best approach to optimally balance pipeline risk (**Table 1**).

Lowering costs, mitigating risks

While biologics – whether it is a biosimilar, biosuperior or the original, innovative compound – are all complex treatments, they do not share the same regulatory pathway to approval or involve the same level of investment or risk.

A first-in-class product is associated with the greatest risk as it requires identifying a new target, and subsequently developing a therapeutic compound for that target and validating the target mechanism for disease intervention in human. All this does come at a price – companies involved in developing innovative, first-in-class biologics such as monoclonal antibodies must employ advanced technologies such as recombinant DNA, and mammalian expression techniques. In addition, it requires manufacturing facilities with greater complexity than what is involved with small molecule drugs. By some estimates, the cost to bring an innovative biologic to market can run as high as $1.2 billion. But consider the rewards – the introduction of the first biologic therapies in oncology,

Table 1

BIOLOGIC	PIPELINE RISK	DEVELOPMENT COST	POTENTIAL BENEFITS
First-in-class	High	High	First-generation therapy with a novel mechanism of action
Biosuperior	Medium	Medium to High	Improvements in key drug attributes (efficacy, safety, dosing) over original brand
Biosimilar	Low	Low to Medium	Lower price versus original innovation

for example, represented a game changer over standard therapies, offering a more targeted approach to cancer management. Rather than killing cells indiscriminately, oncologists now have therapies that can turn off pathogenic pathways, activate apoptosis signalling, or even down regulate signal pathways. Clearly, the stakes to develop first-in-class biologics are high, but so are the potential rewards.

On the opposite side of the spectrum are biosimilars. These compounds are associated with the lowest risk to a pipeline portfolio, as they essentially copy an existing biologic molecule. Sometimes called a 'follow-on biologic', 'subsequent entry biologic' or 'similar biotherapeutic product', a biosimilar is intended to be as much like the original therapy as possible. In recent years, some simple biosimilar drugs, such as insulin, erythropoietin and interferon have been successfully developed and launched. However, for complex biologics, such as monoclonal antibodies or Fc fusion proteins, given their high complexity and the unique manufacturing processes, the pathway to a generic biologic can often be as cumbersome as the original product. Unlike the relatively quick development and approval process for generic pharmaceuticals, most follow-on biologics must undergo clinical trial testing to demonstrate comparability to the original therapy. This includes showing that the profile of the copy exactly replicates, or is at least similar to, the innovator product's characteristics, including pharmacokinetics, mechanism of action and route of administration. There is a risk that subtle changes may cause the generic molecule to perform differently.

Like a biosimilar, a biosuperior drug is developed against an already established biological target that has been validated in human clinical trials. But that is where the similarities end. A biosuperior is intended to have attributes that are better than the first-generation product, rather than being a carbon copy. The overall pipeline portfolio risk with a biosuperior is higher than with a biosimilar, but less than the innovator product because the goal is to demonstrate an improvement over the existing treatment based on already validated targets.

A biosuperior utilises cutting-edge technologies such as protein engineering, and novel drug formulation and delivery approaches to enable its superiority over a first-generation product, possibly improving its efficacy or safety profile or improving administration route or reducing dosing frequency. In particular, a few technologies offer great promise for biosuperior antibodies, including affinity maturation, effector function enhancement, half-life extension through Fc engineering, bi-specific, and antibody-drug conjugate technology. Ideally, a biosuperior has the potential to become a best-in-class product because it is yielding benefits beyond the innovator product. Given these loftier research goals of a biosuperior, R&D costs will run higher than for a biosimilar, although the investment is not nearly as significant as developing a first-generation product.

Finding the right mix

Today, many pharmaceutical companies are racing to become early entrants in the biosimilar marketplace. Biosimilars represent an opportunity for a manufacturer to enter a new category, and realise an economic return with a relatively small investment. At the same time, incorporating biosimilars into a pipeline also reduces the portfolio's overall risk. Currently, there are more than a dozen companies that have developed a biosimilar, or are working on products to enter the biosimilar market.

Biosimilars have become an attractive model for many payers and governments looking for a less costly alternative to the original innovation. While this may appear to be an advantageous way to reduce healthcare costs associated with biologic therapies, the benefits end here. As copycats, biosimilars fall short in offering patients and their physicians with any new, clinically-meaningful benefits beyond the existing therapy. Biosimilars, therefore, allow companies to enter a market and put pricing pressures on competitors without offering much added value for patients. There are strategic alternatives in breaking into a new biologics market that optimise the balance between investment, risk and rewards.

Given the clinical applications, implications for new treatments and potential return on investment, biologics are a growing priority for many drug developers. Some companies, including MedImmune, the global biologics unit of AstraZeneca, are beginning to increase their research and development investment in biosuperiors as part of their overall investment strategy to maintain a sustainable pipeline. These drugs offer stronger, long-term incentives as they have the potential to provide patients with true clinical benefits, whether that is a more effective therapeutic option, a better safety profile, or a more convenient dosing schedule. At the same time, biosuperiors can help to generate a more substantial return on investment for a developer.

With comparative clinical superiority, biosuperiors provide patients, physicians and payers greater value compared to biosimilar products. Biosuperiors strive to be best-in-class products, yet may take less time to pull through the pipeline, compared to first-generation drugs. Although biosuperiors represent a higher risk in investment versus biosimilars, they have the potential to yield greater business benefits, such as market share and profitability.

While research and development programmes will continue to focus on discovering new disease targets and creating first-in-class therapies for patients, it is equally important to find a solid counterbalance to minimise a company's pipeline risk exposure given the high-stakes nature of the industry. Biosimilars and biosuperiors each have their own advantages for a drug manufacturer, as well as the patient and medical communities it serves. But the development of biosuperior drugs truly strikes the right balance between providing life-changing medical treatments for patients and maintaining an innovative pipeline for continued business success. Given the benefits of biosuperiors, from both a business and a clinical standpoint, there is potential to significantly change the treatment paradigm for many disease areas. DDW

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